



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

10/687,706

10/20/2003

Joseph Loscalzo

102258.170 US2

2830

25270 7590 04/17/2008

WILMERHALE/NITROMED
1875 PENNSYLVANIA AVE, NW
WASHINGTON, DC 20006

EXAMINER

SRIVASTAVA, KAILASH C

ART UNIT

PAPER NUMBER

1657

MAIL DATE

DELIVERY MODE

04/17/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/687,706	Applicant(s) LOSCALZO ET AL.	
	Examiner Dr. Kailash C. Srivastava	Art Unit 1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 January 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9, 12, 13 and 16-25 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-9, 12, 13 and 16-25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>01/16/2008</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Amendment and response filed 16 January 2008 to Office Action mailed 26 October 2007 is acknowledged and entered.

Withdrawals to Objections and Rejections

2. In view of remarks filed 16 January 2008, the following objections and rejections in the Office Action mailed 26 October 2007 are hereby withdrawn:

- Objection to Information Disclosure Statement.
- Anticipatory rejection to Claims 1-4, 6-9 and 16-18 under 35 U.S.C. §102(b) as anticipated by Cohn (U.S. Patent 4,868, 179).
- Obviousness rejection to Claims 1-4, 6-9, 12-13 and 16-25 under 35 U.S.C. § 103 (a) as obvious over combined teachings from Cohn (U.S. Patent 4,868, 179) in view of Klemsdal et al. ((1994. A New Isosorbide Dinitrate Extended-Release Formulation: Pharmacokinetic and Clinical Parameters in Patients with Stable Angina Pectoris. Eur. J. Clin. Pharmacol., 47:351-354) with evidence from Wikipedia (Anonymous, Isosorbide mononitrate. From Wikipedia Pages 1-4 Printed 10/18/2007) and further in view of Chobanian et al (U. S. Patent 5,645,839).

Claims Status

3. Claims 10-11, 14-15 and 26-129 remain cancelled.
4. Claim 1 has currently been amended.
5. Claims 1-9, 12-13 and 16-25 are pending and are examined on merits.

Rejections Under 35 U.S.C. § 102(b)

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. In view of amendment to Claim 1 in the Amendment filed 16 January 2008, the following is a new rejection to Claims 1-4, 6-9 and 16-18 under 35 U.S.C. § 102(b).

8. Claims 1-4, 6-9 and 16-18 are rejected under 35 U.S.C. § 102(b) as anticipated by Cohn (U.S. Patent 4,868, 179) with evidence provided by Hunter et al (U.S. Patent 5,716,981 A).

Claims recite a biodegradable, micro- or nanoparticulate sustained release composition comprising a small molecule antioxidant and isosorbide dinitrate, wherein the antioxidant is a hydralazine compound, namely hydralazine hydrochloride. In said composition, the isosorbide dinitrate is in range of 30 milligrams/ day to 160 milligrams/day and hydralazine hydrochloride in range of 30 milligrams to 400 milligrams/day and is in a solid dose as a tablet or capsule. Said composition further comprises a pharmaceutically acceptable carrier.

Regarding Claims 1-4, 6-9 and 16-18, Cohn teaches a composition in form of tablet or capsule, wherein said composition comprises a daily dose in range of 55 milligrams/day to 3, 000 mg/day of hydralazine hydrochloride and 30 milligrams/day to 160 milligrams/day of isosorbide dinitrate (Column, Lines 5-8; Column 3, Lines 19-47). Since the unit dose is in form of capsule and/or tablet, it is solid and is comprised of a pharmaceutical carrier and the composition of each of the components is within the range of the dosage instantly claimed. Please note further that therapeutic, pharmaceuticals encapsulated in a biodegradable, micro- or nano-particulate carriers are well recognized in the pertinent art (See, Hunter et al., Column 52, Line 52 to Column 17, Line 6; especially Column 16, Lines 7 and 37; Column 17, Lines 5-6 and Column 37, Lines 56-61).

Therefore, Cohn anticipates the composition claimed in Claims 1-4, 6-9 and 16-18.

Rejections Under 35 U.S.C. § 103(a)

9. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates

of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

11. In view of amendment to Claim 1 in the Amendment filed 16 January 2008, the following is a new rejection to Claims 1-4, 6-9, 12-13 and 16-25 under 35 U.S.C. §103(a)

12. Claims 1-9, 12-13 and 16-25 are rejected under 35 U.S.C. § 103 (a) as obvious over combined teachings from Cohn (U.S. Patent 4,868, 179) in view of Hunter et al (U.S. Patent 5,716,981 A) and Klemsdal et al. ((1994. A New Isosorbide Dinitrate Extended-Release Formulation: Pharmacokinetic and Clinical Parameters in Patients with Stable Angina Pectoris. Eur. J. Clin. Pharmacol., 47:351-354) with evidence from Wikipedia (Anonymous, Isosorbide mononitrate. From Wikipedia Pages 1-4 Printed 10/18/2007) and further in view of Chobanian et al (U. S. Patent 5,645,839).

Claims recite a biodegradable, micro- or nanoparticulate sustained release composition comprising a small molecule antioxidant and isosorbide dinitrate, wherein the antioxidant is a hydralazine compound, namely hydralazine hydrochloride. In said composition, the isosorbide dinitrate is in range of 30 milligrams/ day to 160 milligrams/day and hydralazine hydrochloride in rang of 30 milligrams to 400 milligrams/day and is in a solid dose as a tablet or capsule. Said composition further comprises a pharmaceutically acceptable carrier. Said composition also comprises an angiotensin converting enzyme (i.e., ACE) inhibitor and may alternatively comprise isosorbide mononitrate. Claims additionally each a method to treat a vascular disease characterized by nitric oxide insufficiency via administering a sustained release composition comprising isosorbide nitrate, hydralazine hydrochloride and an ACE-inhibitor.

Regarding Claims 1-4, 6-9, 12-13 and 16-25, Cohn's teachings with evidence from Hunter et al., have already been discussed *supra*. Cohn, however, does not elaborate on a biodegradable micro- or nanoparticulate sustained released pharmaceutical composition and further a composition comprising an isosorbide mononitrate, or a composition comprising ACE-inhibitor and isosorbide dinirate.

Hunter et al., teach in detail a sustained released, pharmaceutical composition comprising an antioxidant (i.e., ascorbic acid) and isosorbide dinitrate (Column 16, Line 37 and Column 37, Lines 56-61) encapsulated in a biodegradable, nano- or microparticulate pharmaceutical carrier (Column 17, Lines 1-6) applicable for non-angiogenic conditions (Column 15, Line 52 to Column 17, Line 6 and Column 37, Lines 56-61).

Klemsdal et al. teach similar effect of administering either isosorbide dinitrate or isosorbide mononitrate in treating angina pectoris (Figure 1). Furthermore, isosorbide mononitrate “exerts qualitatively similar effects” (See Wikipedia, Pages 1, Lines 36-37). Thus, one skilled in the art will be apprised to substitute isosorbide mononitrate for isosorbide dinitrate, or would even substantiate isosorbide dinitrate with isosorbide mononitrate.

Chobanian et al. teach a composition comprising an ACE inhibitor, a nitric oxide stimulator and at least one pharmaceutically acceptable carrier (Column 3, Lines 55-56) and orally administering said composition to a patient in need thereof (Column 3, Lines 65-66) to treat nitric oxide insufficiency mediated cardiovascular diseases (e.g., arteriosclerotic disorders, secondary hypertension and like; Column 7, Line 60; Column 8, Line 1). Chobanian et al. further teach that said composition comprises an ACE inhibitors (e.g., captopril, laurel, perindopril) and isosorbide dinitrate (Column 4 Lines 45-49 and 58-59). Chobanian et al. even teach additional anti oxidants (e.g., acerbate, tocopherol and β -carotene; Column 4, Lines 63-64). Choninian et al. also teach that the compositions comprising ACE-inhibitors, isosorbide dinitrate and a pharmaceutically acceptable carrier may additionally comprise a variety of agents applicable for cardiovascular disease therapy (e.g., anti-anginal agents, calcium channel blocking agents, vasodilators, antihypertensives among others in form of a tablets, coated tablets, capsules or granules (Column 5, Lines 12-41). Thus, Chobanian et al. clearly teach a composition comprising isosorbide dinitrate with an ACE-inhibitor as well as a method to treat a nitric oxide insufficiency mediated cardiovascular disease.

Thus, at the time, the claimed invention was made, an artisan of ordinary skill would have been motivated to combine the teachings from Cohn according to beneficial teachings from Hunter et al., Klemsdal et al., and Chobanian et al. to obtain a biodegradable, nano-, or microparticulate sustained release formulation comprising a “low molecule” antioxidant and isosorbide dinitrate, wherein said “low molecular weight antioxidant is hydralazine hydrochloride and a method to treat a cardiovascular disease with the application of said composition; because (i) Hunter et al., teach a sustained released, biodegradable, nano-or microparticulate pharmaceutical composition comprising an antioxidant and isosorbide dinitrate, (ii) Klemsdal et al teach that isosorbide mono nitrate and dinitrate produce the same qualitative effect and accordingly one may be substituted for the other and (iii) Chobanian et al. teach a composition comprising isosorbide dinitrate with ACE-inhibitors along with a pharmaceutically acceptable carrier in form of a tablet or capsule and further teach that said composition is orally administered to a patient in need thereof to treat a nitric oxide deficiency mediated cardiovascular disease.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify teachings from Cohn according to beneficial teachings from each one of Hunter et al., Klemsdal et al., and Chobanian et al. to obtain a biodegradable, nano-, or microparticulate sustained release composition comprising isosorbide di nitrate and/or mononitrate with an antioxidant, wherein said antioxidant is hydralazine hydrochloride and an ACE inhibitor with at least one pharmaceutically acceptable carrier to treat a nitric oxide insufficiency-mediated cardiovascular disease; because Hunter et al. teach a biodegradable, nano-, or microparticulate pharmaceutical composition comprising isosorbide dinitrate and an antioxidant for non-angiogenic conditions; Klemsdal et al. teach isosorbide dinitrate may be substituted with isosorbide mononitrate and Chobanian et al teach a composition comprising isosorbide dinitrate and an ACE inhibitor in a pharmaceutically acceptable carrier, wherein said composition is in form of a tablet or capsule. Furthermore, the concentration of isosorbide dinitrate and hydralazine hydrochloride disclosed in the prior art references is within the range that is instantly claimed.

From the teachings of the references cited *supra*, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Prior Art Not Applied

13. The prior art made of record and not relied upon is considered pertinent to Applicants' disclosure.
- Gref, R. et al. 1994. Biodegradable Long-Circulating Polymeric Nanospheres. Science, Volume 263, Pages 1600-1603, March 18. Discusses nanoparticulate pharmaceutical carriers for site-specific drug delivery. These are monodisperse biodegradable nanospheres that entrapped up to 45% by weight of the target drug. Said nanospheres could be freeze-dried.

Conclusion

14. For reasons aforementioned, no Claims are allowed.
15. Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See M.P.E.P. §706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 C.F.R. §1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. §1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kailash C. Srivastava whose telephone number is (571) 272-0923. The examiner can normally be reached on Monday to Thursday from 7:30 A.M. to 6:00 P.M. (Eastern Standard or Daylight Savings Time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Jon Weber can be reached at (571)-272-0925 Monday through Thursday 7:30 A.M. to 6:00 P.M. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding may be obtained from the Patent Application Information Retrieval (i.e., PAIR) system. Status information for the published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (i.e., EBC) at: (866)-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Dr. Kailash C Srivastava/
Examiner, Art Unit 1657/

Kailash C. Srivastava, Ph.D.
Patent Examiner
Art Unit 1657
(571) 272-0923

13 April 2008

/David M. Naff/
Primary Examiner, Art Unit 1657